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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,455	12/28/2001	Yasuaki Itoh	56804 (46342)	5636

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EXAMINER
HADDAD, MAHER M

ART UNIT	PAPER NUMBER
1644	9

DATE MAILED: 02/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,455	ITOH ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *17,20,21 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,18,19,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-24 are pending.

2. Applicant's election of Group I, claims 1-16, 18-19 and 22-23 dawn to a polypeptide comprising amino acid of SEQ ID NO:24, its amide, ester or a salt thereof encoded by a DNA of SEQ ID NO: 23, a recombinant vector, transformant and a method of manufacturing the polypeptide, a kit a pharmaceutical polypeptide and a method of screening using the polypeptide, Applicant further elected SEQ ID NO:24 as the species filed on 12/23/02, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Upon reconsideration Examiner has extended the search to cover SEQ ID NOS: 6, 12, 26, 47 and 49 encoded by SEQ ID NOS: 4, 10, 25, 46 and 48, respectively.

3. Claims 17, 20, 21 and 24 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1-16, 18-19 and 22-23 are under examination as they read on polypeptides of SEQ ID NOS: 6, 24, 12, 26, 47 and 49 encoded by SEQ ID NOS: 4, 23, 10, 25, 46 and 48, respectively, a recombinant vector, transformant and a method of manufacturing the polypeptide, a kit a pharmaceutical polypeptide and a method of screening using the polypeptide.

5. Claim 16 is objected to under 37 CFR § 1.75(c) as being in improper form because a multiple dependent claim cannot depend from two sets of claims drawn to two different features.

6. This application contains an abstract in impropriate format because the abstract contains two paragraphs.

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

7. Applicant's IDS, filed 12/28/01 (Paper No. 2), is acknowledged, however, reference BA abstract was only considered as the English translation was not found. Applicant is invited to produce the English translation.

8. 35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

9. Claims 1-16, 18-19 and 22-23 are rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1 and 7, as written, do not sufficiently distinguish over proteins and nucleic acids as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified" as disclosed on page 15, line 19 of specification. See MPEP 2105.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-16, 18-19 and 22-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) The phrase " substantially the same as" recited in claims 1 and 2 is ambiguous and indefinite because and the metes and bounds of the claimed "substantially the same" is not defined.

B) The term " bearing" in claim 7, line 1 is improper, it is suggested the term be changed to "having".

C) The "The DNA" recited in claims 8-14, line 1 has no antecedent basis in base claim 6. Base claim 1 only recites a polypeptide.

D) Claim 18 provides for the use of the polypeptide, but, since the claim does not set forth any steps involved in the method, it is unclear what method applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. It is unclear how to determine the activity of the polypeptide.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-16, 18-19 and 22-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide sequence of SEQ ID NOS: 24, 6, 26, 12, 49 and 47 their amide or ester or a salt thereof, the nucleic acid of SEQ ID NOS: 23, 4, 25, 10, 48 and 46 encoding the polypeptides, recombinant vector comprising the DNA of SEQ ID NOS: 23, 4, 25, 10, 48 and 46, a method for manufacturing the polypeptide, a method of in vitro screening a compound or its salt that promotes or inhibits the activity of the polypeptides, a kit for screening a compound comprising the polypeptides, and composition comprising the polypeptides, their amide or ester, or a salt thereof.; does not reasonably provide enablement for any "*substantially the same* as" amino acid sequence represented by SEQ ID NO: 24 in claims 1-6, respectively; or any DNA bearing a base sequence encoding the polypeptide of any "*substantially the same* as amino acid sequence represented by SEQ ID NO: 24" in claims 7-13; any recombinant vector comprising the "*substantially the same* as amino acid sequence represented by SEQ ID NO: 24" in claim 14, a method of screening a compound or its salt that promotes or inhibits the activity of the polypeptide or it salt which comprises using the polypeptide its amide or ester or a salt thereof in claim 18, a kit for screening a compound or its salt that promotes or inhibits the activity of the polypeptide, its amide or ester, or a salt thereof, comprising the "substantially the same" polypeptide or its salt of SEQ ID NO: 24 in claim 19, a pharmaceutical comprising the "substantially the same" polypeptide of SEQ ID NO: 24 its amide or ester, or a salt thereof in claim 22, or any agent for the prevention/treatment of bone and joint diseases or pathologic angiogenesis, comprising the "substantially the same" polypeptide, its amide or ester, or a salt thereof of SEQ ID NO:24 in claim 23. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide a sufficient enabling description of the claimed invention. The specification discloses only nucleic acid sequences of SEQ ID NO:23, 4, 25, 10, 48 and 46 encoding the polypeptides of SEQ ID NO:24, 6, 26, 12, 26, 47 and 49 respectively, with a disclosed activity of cell-function-regulating-secretory-protein-i.e.-differentiation,-proliferation, and malignant alteration (e.g., page 3, lines 11-12 and 22-23). The instant claims encompass in their breadth *any* amino acid encoded by any nucleotide, wherein the an amino acid is

"substantially the same" as SEQ ID NO: 24; or a method of screening a compound for promoting or inhibiting the activity of the polypeptide comprising using the polypeptide its amide or ester or a salt thereof, any pharmaceutical comprising the "substantially the same" polypeptide of SEQ ID NO:24; or any agent for (*the prevention/treatment of bone and joint diseases or pathologic angiogenesis*).

There does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the various amino acids and nucleic acids recited in the instant claims. A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance to direct a person of skill in the art to select particular sequences or sequence lengths as essential for regulating cell function. Without detailed direction as to which nucleic acid sequences are essential to the function of the encoded polypeptide, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of nucleic acid sequences encompassed by the instant claims would share the ability to regulate cell function of the encoded polypeptide of SEQ ID NOS:24, 6, 26, 12, 49 and 47, other than the nucleic acid of SEQ ID NOS:23, 4, 25, 10, 48, and 46, respectively.

Because of this lack of guidance, an undue experimentation would be required to determine which modifications would be acceptable to retain occluding structural and functional activity, and the fact that the relationship between the sequence of a protein/peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Ngo *et al* in the Protein Folding problem and Tertiary Structure prediction, 1994, Merz *et al.*, (ed), Birkhauser, Boston, MA, pp.433 and 492-495), it would require an undue amount of experimentation for one of skill in the art to arrive at the claimed polypeptides encompassed by the claimed invention

Attwood (Science 2000; 290:471-473) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech. 2000; 18(1):34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). Finally, even single amino acid differences can result in drastically altered functions between two proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). Thus it is unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences.

The skilled artisan would not reasonably expect a polypeptide having anything less than 100% identity *over the full length of SEQ ID NO:24* to *share the same function*. The recitation "substantially the same" is not seen as providing a requisite functional activity for the amino acid encoded by the nucleic acid because of the unpredictability of such sequence similarity would provide the same functional activities. Thus the recitation of substantially the same language, in the absence of *a testable function* and limitations regarding the *sequence length over which the similarity is required*; does not allow the skilled artisan to make and use the polypeptides and the encoding nucleic acids commensurate in scope with the instant claims without undue experimentation.

Also, at issue is whether or not the claimed composition would function as pharmaceutical composition. In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the pharmaceutical composition as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed pharmaceutical composition are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success.

Further, at issue is whether or not the claimed agent would function to prevent/treat " bone and joint diseases or pathologic angiogenesis". The specification on page 103 under Example 8, discloses the suppressive effect of MLP protein on cartilage differentiation using ATDC5 cells. The exemplification is drawn to the suppressed expression of marker genes such as aggrecan, type II collagen, type X collagen, which correlate with increased expression during differentiation. While such *in vitro* assay may provide an indication that particular compositions are appropriate to target for *further experimental consideration*. Applicant's disclosure does not appear to have provided the skilled artisan with sufficient guidance and support as how to extrapolate data obtained from *in vitro* assay to the development of effective *in vivo* human therapeutic methods, commensurate in scope with the claimed invention.

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since no animals were used as model system to prevent/treat bone and joint diseases or pathologic angiogenesis. It is not clear that reliance on the *in vitro* suppression of certain gene marker of differentiation accurately reflects the relative mammal efficacy of the claimed therapeutic strategy. The specification does not adequately teach how to effectively prevent/treat bone and joint diseases or pathologic angiogenesis or reach any therapeutic endpoint in mammals by administrating the therapeutic agent. The specification does not teach how to extrapolate data obtained from an in vitro assay studies to the development of effective in vivo mammalian therapeutic treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the therapeutic agent exemplified in the specification.

On the basis of the disclosed apparent in vitro observation alone, applicant concludes that the scope of the MLP defined by sequences encompassed by the claimed invention can have biological activity to prevent/treat bone and joint diseases or pathologic angiogenesis and be provided as pharmaceutical compositions to subjects including human.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

14. Claims 1-16, 18-19 and 22-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of the polypeptide sequence of SEQ ID NOS: 24, 6, 26, 12, 49 and 47 their amide or ester or a salt thereof, the nucleic acid of SEQ ID NOS: 23, 4, 25, 10, 48 and 46 encoding the polypeptides, recombinant vector comprising the DNA of SEQ ID NO: 23, 4, 25, 10, 48 and 46, a method for manufacturing the polypeptide, a method of in vitro screening a compound or its salt that promotes or inhibits the activity of the polypeptides, a kit for screening a compound comprising the polypeptides, and composition comprising the polypeptides, their amide or ester, or a salt thereof.

Applicant is not in possession of any "*substantially the same* as" amino acid sequence represented by SEQ ID NO: 24 in claims 1-6, respectively; or any DNA bearing a base sequence encoding the polypeptide of any "*substantially the same* as amino acid sequence represented by SEQ ID NO: 24" in claims 7-13; any recombinant vector comprising the "*substantially the same* as amino acid sequence represented by SEQ ID NO: 24" in claim 14, a method of screening a compound or its salt that promotes or inhibits the activity of the polypeptide or it salt which comprises using the polypeptide its amide or ester or a salt thereof in claim 18, a kit for screening a compound or its salt that promotes or inhibits the activity of the polypeptide, its amide or ester, or a salt thereof, comprising the "substantially the same" polypeptide or its salt of SEQ ID NO: 24 in claim 19, a pharmaceutical comprising the "substantially the same" polypeptide of SEQ ID NO: 24 its amide or ester, or a salt thereof in claim 22, or any agent for the prevention/treatment of bone and joint diseases or pathologic angiogenesis, comprising the "substantially the same" polypeptide, its amide or ester, or a salt thereof of SEQ ID NO:24 in claim 23.

Applicant has disclosed only amino acid sequences of SEQ ID NO: 24, 6, 26, 12, 49 and 47 and the nucleic acid sequence of SEQ ID NO: 23, 4, 25, 10, 48 and 46; therefore, the skilled artisan cannot envision all the contemplated amino acid and nucleic acid sequence possibilities recited in the instant claims. Consequently, conception cannot

be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
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February 24, 2003

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